ACE High? Reshuffling the Deck in the Management of Heart Failure

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Disclosure
Nothing to disclose
PARADIGM-HF

**Inclusion Criteria**
- Age ≥ 58 years
- NYHA functional class II-IV
- Ejection fraction ≤ 40%
- BNP ≥ 150 pg/mL or BNP > 200 pg/mL and hospitalization for heart failure in prior 12 months
- Stable dose of ACE inhibitor or ARB (equivalent to enalapril 30 mg/day) and beta blocker for ≥ 4 weeks

**Select Exclusion Criteria**
- Symptomatic hypotension
- Systolic blood pressure < 100 mmHg
- Estimated GFR < 30 mL/min/1.73 m²
- Serum K⁺ > 5.2 mEq/L
- Prior intolerance to target doses of ACE inhibitors or ARBs
- Known history of angioedema

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**PARADIGM-HF**

**Reason for Discontinuation**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Enalapril Run-in</th>
<th>LCZ696 Run-in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal Laboratory/Tests</td>
<td>58 (0.6%)</td>
<td>52 (0.6%)</td>
</tr>
<tr>
<td>Withdraw Consent</td>
<td>100 (1.0%)</td>
<td>100 (1.0%)</td>
</tr>
<tr>
<td>Protocol-Related Issue</td>
<td>146 (1.6%)</td>
<td>146 (1.6%)</td>
</tr>
<tr>
<td>Death</td>
<td>43 (0.5%)</td>
<td>43 (0.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>70 (0.8%)</td>
<td>70 (0.8%)</td>
</tr>
</tbody>
</table>

**Baseline Medication Use**

<table>
<thead>
<tr>
<th>Baseline Medication Use</th>
<th>Enalapril (n=4212)</th>
<th>LCZ696 (n=4187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretrial use of an ACE inhibitor (%)</td>
<td>77.9%</td>
<td>78.0%</td>
</tr>
<tr>
<td>Pretrial use of an ARB (%)</td>
<td>22.1%</td>
<td>22.3%</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>50.1%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Aldosterone antagonist (%)</td>
<td>57.0%</td>
<td>57.0%</td>
</tr>
<tr>
<td>Diuretic (%)</td>
<td>31.2%</td>
<td>29.2%</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator (%)</td>
<td>14.7%</td>
<td>14.9%</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy (%)</td>
<td>6.7%</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

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**PARADIGM-HF**

**Baseline Characteristic (Select)**

<table>
<thead>
<tr>
<th>Baseline Characteristic (Select)</th>
<th>Enalapril (Pretrial)</th>
<th>LCZ696 (Pretrial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.8 ± 11.3</td>
<td>63.8 ± 11.5</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>22.6%</td>
<td>22.6%</td>
</tr>
<tr>
<td>White, Black, Asian (%)</td>
<td>66.9%, 5.3%, 18.6%</td>
<td>66.9%, 5.3%, 18.6%</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121 ± 15</td>
<td>122 ± 15</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.12 ± 0.3</td>
<td>1.13 ± 0.3</td>
</tr>
<tr>
<td>NYHA functional class II, III (%)</td>
<td>69.3%, 24.7%</td>
<td>71.0%, 23.5%</td>
</tr>
<tr>
<td>Left-ventricular ejection fraction (%)</td>
<td>29.4 ± 6.3</td>
<td>29.6 ± 6.4</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/mL)</td>
<td>251 (153-462)</td>
<td>255 (155-446)</td>
</tr>
<tr>
<td>Prior hospitalization for heart failure (%)</td>
<td>65.3%</td>
<td>65.3%</td>
</tr>
</tbody>
</table>
**Primary Composite Endpoint**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Enalapril</th>
<th>LCZ696</th>
<th>logRR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint (death from cardiovascular causes or first hospitalization for worsening heart failure, NYHA Class IV)</td>
<td>112 (24.9%)</td>
<td>96 (22.6%)</td>
<td>0.43 (0.29-0.65)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes (NYHA Class IV)</td>
<td>63 (14.5%)</td>
<td>52 (12.5%)</td>
<td>0.71 (0.49-1.02)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Fewer hospitalizations for worsening heart failure (NYHA Class IV)</td>
<td>180 (42.1%)</td>
<td>129 (31.2%)</td>
<td>0.73 (0.58-0.93)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*In a randomized trial comparing LCZ696 with enalapril, patients treated with LCZ696 had a statistically significant reduction in primary endpoint, death from cardiovascular causes or first hospitalization for worsening heart failure (NYHA Class IV). The incidence of death from cardiovascular causes was lower with LCZ696 compared to enalapril. In addition, LCZ696 was associated with fewer hospitalizations for worsening heart failure (NYHA Class IV) compared to enalapril.

**PARADIGM-HF**

**Secondary Endpoints**

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Enalapril</th>
<th>LCZ696</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>83 (29.8%)</td>
<td>73 (26.7%)</td>
<td>0.84 (0.76-0.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in LVEF</td>
<td>3.6 (±3.0)</td>
<td>3.3 (±3.0)</td>
<td>1.04 (0.99-1.09)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New-onset atrial fibrillation</td>
<td>8 (2.1%)</td>
<td>8 (2.1%)</td>
<td>0.97 (0.72-1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in renal function*</td>
<td>10 (2.5%)</td>
<td>9 (2.3%)</td>
<td>0.86 (0.65-1.13)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*Defined as an >10% decrease in GFR or a decrease in GFR of >10 mL/min/1.73 m² to <60 mL/min/1.73 m².

**Follow-Up Analyses of PARADIGM-HF**

- Progression analysis showed a 23% reduction in heart failure hospitalizations with LCZ696 (851 vs. 1079, p<0.001).
- Mode of death analysis showed reductions with LCZ696 driven by sudden cardiac death (6.0% vs. 7.4%, p=0.008).
- Age analysis showed consistent benefit of LCZ696 across subgroups of <55, 55-65, 65-74, and ≥75 years of age.

**Cost Effectiveness and Value**

- Average wholesale price: $5,400
- Cost-effectiveness: $50,915 per QALY gained for those with average benefit for over 5 years.
- Cost-effectiveness: $100,000 per QALY gained for those benefiting for 3.3 years or less.
- To not exceed the growth of health care costs (in proportion with US economic growth), would need to be $4,168 or less.

**Remaining Controversies**

- Suboptimal background therapy
- Efficacy and safety in specific subpopulations
  - Black patients
  - NYHA Class I, IV, and ADHF
- Patients not previously on ACE inhibitors or ARBs
- Impact on blood pressure
- ProBNP and NT-proBNP monitoring
- Off-target effects of neprilysin inhibition

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**Notes:**

ACE inhibitors | Angiotensin Receptor Blockers | Nebivolol / Angiotensin Receptor Blockers
--- | --- | ---
• ATLAS | • CHARM Overall | • PARADIGM-HF
• CHARM Added | • CHARM Added |
• CONSENSUS II, III | • CHARM Preserved |
• ELITE I, II | • CHARM Alternative |
• OPTIMAAL* | • ELITE I, II |
• SOLVD | • HEAAL |
• SAVE* | • OPTIMAAL* |
• TRACE* | • VAL-HEFT |
• V-HFRT II | • VALIANT* |

*Denotes trial of left ventricular dysfunction after myocardial infarction
ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; NSAID: nonsteroidal anti-inflammatory drug; OATP: organic anion transport protein, P: peak; OATP1B1: organic anion transporting polypeptide 1B1; OATP1B3: organic anion transporting polypeptide 1B3; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; NR: not reported; OATP: organic anion transporting protein; Y: year.

Sacubitril/Valsartan

Approved Indications
• To reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic NYHA Class II-IV heart failure with reduced ejection fraction
• Administered in conjunction with other heart failure therapies in place of an ACE inhibitor or ARB

Contraindications
• Patients with hypersensitivity to sacubitril or valsartan
• In patients with a history of angioedema related to previous ACE inhibitor or ARB therapy
• Concomitant ACE inhibitor use, must allow for 36-hour washout
• Concomitant aliskiren in patients with diabetes

Drug-Drug Interactions
• Other RAAS inhibitors
• Potassium-sparing diuretics
• NSAIDs
• Lithium
• Inhibits OATP1B1 and OATP1B3 transporters but effects unknown
• Minimal CYP450 involvement

Precautions/Warnings
• Pregnancy (boxed warning)
• Breastfeeding not recommended
• Angioedema
• Hypotension
• Impaired renal function
• Hyperkalemia

Proposed Place in Therapy for Sacubitril/Valsartan

Sacubitril/Valsartan

Population | Initial Dose
--- | ---
ACI inhibitor equivalent to enalapril > 10 mg/day, or ARB equivalent to valsartan > 160 mg/day | 49/53 mg twice daily
Naive to ACE inhibitor or ARB, or ARB equivalent to enalapril ≤ 10 mg, or ARB equivalent to valsartan ≤ 80 mg/day | 24/26 mg twice daily
Severe renal impairment (GFR < 30 mL/min/1.73 m²) | 24/26 mg twice daily
Moderate hepatic impairment (Child-Pugh B) | 24/26 mg twice daily

Titratio Schedule: Double the dose of sacubitril/valsartan every 2-4 weeks as tolerated to a target dose of 97/103 mg twice daily

Other Updates in Heart Failure
• Approval of ivabradine to prevent hospitalization in patients with heart failure with reduced ejection fraction and normal sinus rhythm with heart rate ≥ 70 beats per minute on maximally-tolerated dose of beta blocker
• Long-acting nitrates shown not to be beneficial in heart failure with preserved ejection fraction